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α_{1D} -Adrenoceptors are responsible of the high sensitivity and the slow kinetic of adrenergic contraction in conductance arteries

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BACKGROUND: Vascular α_1 adrenoceptor (α_1-AR) subtypes may affect compliance of large and poorly innervated conductance vessels (α_{1D}), as well as redistribution of blood flow through the well innervated distributing arteries (α_{1A}). There are marked differences between subtypes in sensitivity to agonists and second messenger generation, being the α_{1D} the most sensitive with the lower efficacy. Furthermore, α_{1D}-AR acts as "*constitutively active*" receptor in conductance vessels maintaining an increased vascular tone after removing the adrenergic stimulus.

AIMS: To analyze the kinetic of the contractile response and the intracellular signals elicited by α_1-subtypes in two different vessels, aorta (α_{1D}-subtype) and tail artery (α_{1A}-subtype).

METHODS: Tissues were obtained from male Wistar rats or genetically engineered mice (α_{1B}-KO, α_{1D}-KO and $\alpha_{1B/D}$-KO) and their controls (WT). Results of isometric contractility studies were compared with analysis of the [^{3}H] inositol phosphates (IPs) accumulation and ERK1/2 phosphorylation after adrenergic stimulus in the same vessels.

RESULTS: Cumulative concentration-response curves to noradrenaline (NA, 1nM-100μM) elicited a concentration-dependent ERK1/2 phosphorylation, [^{3}H]-IPs accumulation and contractile response in both rat aorta and tail artery. A higher potency (pD_2) of NA together with a lower response was obtained in aorta *vs.* tail artery. In α_{1D}-KO mice the pD_2 value of NA was markedly reduced in aorta and only slightly diminished in tail artery. No significant change in the potency of NA was observed in aortic rings from α_{1B}-KO mice but the magnitude of the response was lower. There is a great loss in the contractile response to NA in $\alpha_{1B/D}$-KO mice. The slow disappearance of the adrenergic contraction after removal of the agonist in rat aorta was not affected by preincubation (15min) with 100nM 5-methylurapidil (α_{1A} selective ligand), but 10nM BMY7378 (α_{1D} selective ligand) induced a faster recovery of the basal tone. In rat tail artery, no significant changes were observed, but NA-induced contraction returns faster than in aorta to basal levels after agonist removal. In aorta from α_{1D}-KO mice, the recovery of basal tone after NA-removal was faster than in WT. By the contrary, the return to the baseline was markedly slower in aorta from α_{1B}-KO mice. These results suggest an involvement of α_{1D}-subtype in the slow recovery of basal tone observed in rat aorta, but not in tail artery, when the agonist was removed. This characteristic could be attributed to the constitutive activity exhibited by the α_{1D}-AR in aorta, as we can evidence by IPs accumulation and increased contractile tone observed after removal of the agonist. The spontaneous increase in tone after removal of NA that evidences the constitutive activity of α_{1D}-AR in rat aorta α_{1B}-KO or WT mice, was not observed in tail from rat and aorta from α_{1D}-KO and $\alpha_{1B/D}$-KO mice, confirming the peculiar behavior of the α_{1D}-subtype.

CONCLUSION: α_{1D}-AR, exhibit a higher sensitivity and lower efficacy to NA-activation and remains active after removal of the agonist, sustaining the adrenergic response and avoiding abrupt changes of vessel caliber in conductance arteries.

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